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U.S. FOOD & DRUG ADMINISTRATION

14. juni 2018

Siri & Glimstad LLP

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Som svar henvises til fil: **2018-3994**

Kære hr. Siri,

Dette er et svar på din anmodning i henhold til Freedom of Information Act (FOIA) dateret 8. maj 2018, hvori du anmodede om "Dokumenter, der er tilstrækkelige til at identificere ingredienserne i 'placebo' i de kliniske forsøg før godkendelse, der er identificeret i afsnit 6.1 i indlægssedlen til RotaTeq." Din anmodning blev modtaget i Center for Biologics Evaluation and Research (CBER) den 14. maj 2018.

I vores telefonsamtale den 25. maj 2018 blev det aftalt, at CBER ville give dig forsiden, relevante indholdsfortegnelser og siderne, der omhandler ingredienserne i placebo, fra de 3 responsive kliniske forsøgsrapporter relateret til de forsøg, der er omtalt i afsnit 6.1 i indlægssedlen til produktet.

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Fru Catherine Teti,

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for Biologisk Evaluering og Forskning (CBER)
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8079 eller via e-mail på John.Hyder@fda.hhs.gov.

Med venlig hilsen,

Beth A. Brockner Ryan -S

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Beth Brockner Ryan
Chef, afdeling for adgangsretssager og informationsfrihed

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Reference P006

MRL Clinical Study Report, Multicenter Study: Safety and Efficacy of Pentavalent (G1, G2, G3, G4, and P1) Human-Bovine Ressortant Rotavirus Vaccine in Healthy Infants (Protocol 006)

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CLINICAL STUDY REPORT

Safety and Efficacy of Pentavalent (G1, G2, G3, G4, and P1) Human-Bovine Ressortant Rotavirus Vaccine in Healthy Infants

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VAO016M001, V260 VAO016M002, V260 VAO016M003, V260 VAO016M004, V260 VAO017N001,V260 VAO017N002, V260 VAO017N003, V260 VAO021R001), when fully characterized, contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium phosphate, approximately (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate-80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an aggregate potency ranging from $67.2x10^6$ to $124x10^6$ infectious units (IU)/dose in approximately 2 mL of buffer/stabilizer. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) mg/dose. Trace components of fetal bovine serum may have also been present. The stability of RotaTeq™ was assessed at predefined evaluation points throughout the study.

Placebo (Lot Numbers: PV260 VAO005A001, PV260 VAO006A001, PV260 VAO006A002, PV260 VAO006A003, PV260 VAO006A004, PV260 VAO009A001, PV260 VAO009A002, PV260 VAO009A003, PV260 VAO009A004, PV260 VAO009A005, PV260 VAO009A006, PV260 VAO009A007, PV260 VAO009A008, PV260 VAO009A009, PV260 VAO0015A001, PV260 VAO0015A002, PV260 VAO0015A003, PV260 VAO0015A004, PV260 VAO0015A005, PV260 VAO0015A007, PV260 VAO022P001) contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, and no greater than (b) (4) mg of polysorbate-80.

For a subset of subjects in the United States (U.S. Concomitant Use Cohort), Merck also provided the licensed pediatric vaccines that were administered concomitantly (same day) with RotaTeq™ or placebo, which included COMVAX™, INFANRIX™, IPOL™, and PREVNAR™. These vaccines were administered at a dose of 0.5 mL.

COMVAX™ (Lot Number: 1076L) was supplied in 0.5-mL single dose vials. INFANRIX™ (Lot Numbers: DTPA524A2, DTPA572A2, DTPA575A2) was supplied in 0.5-mL single-dose vials.

IPOL™ (Lot Numbers: T1153-2 and T1189-2) was supplied in prefilled syringes and/or multidose vials, 0.5-mL per dose.

PREVNAR™ (Lot Numbers: 491-171 and 491-178) was supplied in 0.5-mL single-dose vials. PREVNAR™ was in short supply over the course of the study. When not available for Merck to provide, the study sites were permitted to administer PREVNAR™ from their supply. If PREVNAR™ was provided locally by the physician, the single panel, open label was not used. The lot number and expiration date were to be recorded.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo.

EVALUATION CRITERIA:

Efficacy: The case definition for rotavirus gastroenteritis required subjects to meet both of the following criteria: (1) 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms. All rotavirus-positive stools were evaluated for serotype identification by polymerase chain reaction (PCR). Only naturally-occurring rotavirus AGEs caused by the composite of the human rotavirus G-serotypes in the vaccine (G1, G2, G3, and G4) occurring

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5.4.2 Identity of Clinical Supplies

5.4.2.1 RotaTeq™ and Placebo

Each dose of RotaTeq™ contained human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final aggregate dose range of approximately 67.2 x 10^6 to 124 x 10^6 IU/dose in approximately 2.0 mL of buffer/stabilizer. The potencies of the individual human-bovine reassortants were determined via the Multivalent Quantitative Polymerase Chain Reaction Assay (M-QPA). A description of this assay can be found in Section II.11.12.1. The vaccine was a buffered, liquid product that was originally stored at 2° to 8°C[1]. The formulation used in this study, when fully characterized, contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium phosphate, approximately (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate 80. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) mg/dose. Trace components of fetal bovine serum may have also been present. The stability of RotaTeq™ was assessed at predefined evaluation points throughout the study.

The placebo was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, and no greater than (b) (4) mg of polysorbate 80.

RotaTeq™ or placebo was packaged in 2 different ways for this study including vials and dose packages. The dose packages consisted of labeled foil pouches containing oral dosing tubes. Initially, the clinical materials (RotaTeq™ or placebo) were packaged in 6.0-mL labeled vials containing approximately 2.5 mL of product. Two (2) mL of RotaTeq™ or placebo were drawn up from the vial using a syringe. The needle was removed from the syringe and the vaccine was dispensed orally to the infant. During the course of the study, 5.5-mL labeled oral dosing tubes containing approximately 2.16 mL of product and designed to deliver approximately 2.0 mL were introduced. These dosing tubes represent the final container for RotaTeq™ intended for market. The study provided the opportunity to test the final oral dosing tubes in the clinic. The tubes had a twist-off cap. The cap was removed and the vaccine was delivered orally to the infant directly from the tube. Regardless of the container for clinical materials, approximately 2.0 mL of RotaTeq™ or placebo was administered to all subjects under double-blinded conditions (see Section II.5.4.5).

[1] At the time of the Protocol Amendment 006-01[3.3.2], (b) (4) (b) (4)

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1.1.19	Santssham M, Moulton LH, Reid R, Croll J, Weatherbolt R, Ward R, et al. Efficacy and safety of high-dose rhesus-human reassortant rotavirus vaccine in Native American populations. J Pediatr 1997;131(4):632-8.	1696
1.1.20	Pittman M. The concept of pertussis as a toxin-mediated disease. Pediatr Infect Dis J 1984;3(5):467-86.	1703
1.1.21	Robbins JB, Pittman M, Trollfors B, Lagergard TA, Taranger J, Schneerson R. Primum non nocere: a pharmacologically inert pertussis toxoid alone should be the next pertussis vaccine. Pediatr Infect Dis J 1993;12(10):795-807.	1723
1.1.22	Trollfors B, Taranger J, Lagergård T, Lind L, Sundh V, Zackrisson G, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. N Engl J Med 1995;333:1045-50.	1736
1.1.23	Liese JG, Meschievitz CK, Harzer E, Froeschle J, Hosbach P, Hoppe JE, et al. Efficacy of a two-component acellular pertussis vaccine in infants. Pediatr Infect Dis J 1997;16(11):1038-44.	1742
1.1.24	Lynn F, Reed GF, Meade BD. Collaborative study for the evaluation of enzyme-linked immunosorbent assays used to measure human antibodies to bordetella pertussis antigens. Clin Diagn Lab Immunol 1996;3(6):689-700.	1749
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MERCK RESEARCH LABORATORIES

V260
Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine for Oral Administration

CLINICAL STUDY REPORT
I. SYNOPSIS

Quadrivalent Vaccine Containing Serotypes G1, G2, G3, and P1

PROTOCOL TITLE/NO.: Safety, Tolerability, and Immunogenicity of Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine in Healthy Adults #001

INVESTIGATOR(S)/STUDY CENTER(S): Paul A. Offit, M.D., Philadelphia, PA, U.S.A.

PRIMARY THERAPY PERIOD: 19-Jun-1993 to 08-Jul-1993; Clinical Data Cutoff Date: 04-Dec-1996; Serology Cutoff Date: 11-Nov-1996; Study Completion Date: 08-Jul-1993.

CLINICAL PHASE: I

DURATION OF TREATMENT: Single dose/14-day follow-up.

OBJECTIVE(S): Primary Objective: To determine if the vaccine is safe in healthy immune adults. Secondary Objective: To investigate immune responses after a single dose of quadrivalent vaccine when administered orally to healthy adults.

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial.

SUBJECT ACCOUNTING:

	Rotavirus Vaccine	Placebo
ENTERED: Total	20	11
Male (age range-years)	10 (22 to 40)	5 (21 to 42)
Female (age range-years)	10 (19 to 47)	6 (22 to 34)
COMPLETED:	19	11
DISCONTINUED: Total	1	0
Clinical adverse experience	0	0
Laboratory adverse experiences	0	0
Refused further participation	1	0

DOSAGE/FORMULATION NOS.: Regimen: A 1.0-mL dose of vaccine/placebo orally administered, following an 8-hour overnight fast. One-half hour before administration, subjects were given 4 teaspoons of MAALOX™ (magnesia alumina oral suspension antacid, Novartis Consumer Health, Inc.) to ensure uniform gastric buffering and were asked to refrain from eating for 1 hour after administration of vaccine/placebo. Clinical Material: Quadrivalent human-bovine rotavirus reassortant vaccine, Lot 1340A/C-Y560A, 1.2-mL vial. This vaccine contained serotypes G1, G2, G3, and P1 each with an estimated final titer of 1 x 10^7 plaque-forming units (PFU)/mL in (b) (4) Medium (b) (4) (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4). Placebo, Lot 1341/C-Y561, 1.2-mL vial. This placebo contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4)

DIAGNOSIS/INCLUSION CRITERIA: Healthy adults 18 years of age or older who had no: known hypersensitivity to any component of the rotavirus vaccine, e.g., (b) (4); known or suspected impairment of immunologic function; fever, ≥100°F (oral) at the time of immunization; clinical evidence of chronic or active gastrointestinal illness prior to immunization; other vaccines given within 14 days prior to administration of study vaccine; history of drug or alcohol abuse. Subjects were not pregnant or expecting to conceive during the study period. Subjects must have agreed to use an acceptable method of birth control for 2 weeks after the immunization. Abstinence was considered an acceptable method of birth control. Subjects did not have any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA: Immunogenicity Evaluation: Serum neutralizing antibody levels (for each of G1, G2, G3, P1, bovine WC3 strain, and human W179 strain specificities). Safety Evaluation: Incidence of serious vaccine-related adverse experiences (Days 0 to 14 postvaccination); fecal vaccine virus shedding (Days 2 to 7 postvaccination); temperature elevations (Days 0 to 14 postvaccination); and serum alanine transaminase (ALT) levels (Days 0 and 14 postvaccination).

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CSR SYNOPSIS (CONT.)
Protocol 002

V260
Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine.
Oral Rotavirus Gastroenteritis

DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each dose was 1.0 mL of quadrivalent G1, G2, G3, and P1 human-bovine reassortant rotavirus vaccine or placebo. Dose 1 was given on Day 0, Dose 2 was given 6 to 8 weeks after Dose 1, and Dose 3 was given 6 to 8 weeks after Dose 2.

Clinical Trial Material: G1, G2, G3, and P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of 4 X 10^7 plaque-forming units (PFU), Lot No. 1340A/C-Y560A. Placebo represented buffer alone; i.e., without quadrivalent human-bovine rotavirus reassortants, Lot No. 1341/C-Y561. Vaccine and placebo contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4). Trace components of fetal bovine serum and (b) (4) saline may have been present in the vaccine and placebo.

CLINICAL MATERIAL:

Vaccine	Lot Number-Fill Number	Dosage	Potency (PFU/dose)	Package
Live rotavirus vaccine	1340A/C-Y560A	1.0 mL	4 x 10^7	Code-labeled vial kept at (b) (4)
Placebo	1341/C-Y561	1.0 mL	0	Code-labeled vial kept at (b) (4)

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 2 to 6 months of age who had no known or suspected impairment of immunologic function; no prior administration of any rotavirus vaccine; no fever (defined as a rectal temperature of ≥100.4°F) at the time of immunization; no history of chronic diarrhea or failure to thrive; no clinical evidence of active gastrointestinal disease; no other vaccines given within (+/-) 14 days of any dose of vaccine; no condition that, in the opinion of the investigator, could have interfered with the evaluation of the study objectives; and no infant who resided in a household with an immunocompromised individual.

EVALUATION CRITERIA: **Efficacy:** The case definition for rotavirus gastroenteritis was that a subject must have met both of the following criteria: (1) ≥3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting. (2) Rotavirus must have been identified in a stool specimen taken within 14 days of the onset of symptoms. **Immunogenicity:** Serum samples, taken Predose 1 and Postdose 3, were tested by enzyme immunoassay (EIA) for serum neutralizing antibody (SNA) against G1, G2, G3, P1a, P1G1, G6, and P7. Serum was also tested for anti-rotavirus IgA and IgG. Stool samples, taken Predose 1 and Postdose 3, were tested for fecal anti-rotavirus IgA and total fecal IgA, as well as for fecal neutralizing antibody (FNA) against G1, G6, P1a, and P7. **Safety:** The subjects' parents/guardians were asked to record any adverse experiences that occurred within 14 days after any vaccination. Temperatures were recorded daily for 7 days after each administration of vaccine/placebo. Stool samples for viral shedding were obtained from all participants between Day 3 and Day 5 after Dose 1. In addition, the Philadelphia study site collected stool samples for vaccine viral shedding 1 to 2, 3 to 5, 7 to 9, and ~15 days following each dose.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The primary efficacy hypothesis that the quadrivalent rotavirus vaccine provides efficacy against rotavirus disease throughout one rotavirus season was tested using an exact conditional procedure. The primary hypothesis in the protocol refers to 80% efficacy, which is the expected efficacy that was used for power and sample size calculations; however, the primary hypothesis was tested for vaccine efficacy >0.0% relative to placebo, as noted in the Data Analysis Plan (DAP). A point estimate and exact two-sided 95% confidence interval for vaccine efficacy were also calculated. In order for the quadrivalent rotavirus vaccine to be declared efficacious (i.e., in order to reject the null hypothesis), the lower bound on the confidence interval for vaccine efficacy had to exceed 0%. If there were 160 evaluable infants per group, and assuming that the true incidence of disease in the placebo group would be 10% and that the vaccine would be 80% efficacious in the prevention of rotavirus disease, there would be 80% power to reject the primary null hypothesis. One hundred eighty (180) evaluable infants per group would provide 80% power with an attack rate as low as 9% in the placebo group.

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MERCK RESEARCH LABORATORIES

CSR SYNOPSIS (CONT.)
Protocol 003

V260
G1 G2 Reassortant Rotavirus
Vaccine Live (Human-Bovine)
Oral
Rotavirus Gastroenteritis

SUBJECT ACCOUNTING:

	Rotavirus (G1, G2) Vaccine				Placebo (Groups 2, 4, 6, and 8 Combined)
	1.0 mL – No Buffer (Group 1)	1.0 mL – 1x Buffer (Group 3)	2.5 mL – 1x Buffer (Group 5)	1.0 mL – Conc. Buffer (Group 7)	
ENTERED: Total	142	150	147	142	150
Male (age range—weeks)	64 (8 to 21)	74 (8 to 21)	76 (6 to 21)	77 (8 to 21)	79 (8 to 21)
Female (age range—weeks)	78 (6 to 21)	76 (8 to 21)	71 (7 to 21)	65 (8 to 21)	71 (8 to 21)
COMPLETED:	136	138	137	132	138
DISCONTINUED: Total	6	12	10	10	12
Clinical adverse experience	0	1	0	2	2
Refused further participation	3	6	6	5	6
Lost to follow-up	3	5	4	3	4

DOSAGE/FORMULATION NOS.: Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of administration was either 1.0 mL or 2.5 mL, depending upon the subject's group assignment. Each dose was provided under the following schedule:
Dose 1, given on Day 0.
Dose 2, given between Days 42 and 56.
Dose 3, given between Days 84 and 98.

Group	Prefeeding	Vaccine Vol (mL)	Buffer/Stabilizer	PFU/Dose
1	Yes	1.0	None	1x 10^7 PFU
2†	Yes	1.0	None	0
3	No	1.0	1x	1x 10^7 PFU
4†	No	1.0	1x	0
5	No	2.5	1x	1x 10^7 PFU
6†	No	2.5	1x	0
7	No	1.0	Concentrate	1x 10^7 PFU
8†	No	1.0	Concentrate	0

† Placebo.

CLINICAL MATERIAL: G1 and G2 human-bovine reassortant rotavirus vaccine, a live virus vaccine, Lots No. 1507/W-D152, 1493/W-C971, 1494/W-C972, and 1495/W-C973. The vaccine contained serotypes G1 and G2, each with an estimated final titer of 5 x 10^6 PFU/reassortant or a total of 1x10^7 PFU G1 and G2 human-bovine rotavirus reassortant vaccine per dose, in (b) (4) Medium (b) (4) (b) (4). Placebo represented buffer alone; i.e., without rotavirus vaccine, Lots No. 1506/W-D151, 1489/W-C967, 1490/W-C968, and 1491/W-C969.

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MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

V260
G4 Human-Bovine Reassortant
Rotavirus Vaccine, Oral
Rotavirus gastroenteritis

PROTOCOL TITLE/NO.: Safety and Tolerability of Oral, Live G4 Human-Bovine Reassortant Rotavirus Vaccine in Healthy Adults and Healthy Infants #004

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (02) U.S.

PRIMARY THERAPY PERIOD: 19-Mar-1998 to 07-Jul-1998 (last dose of therapy).
Study completed: 18-Aug-1998.
Clinical Case Report Form and Laboratory Data In-House Cut-off Date: 10-Sep-1999.

CLINICAL PHASE: IIb

DURATION OF TREATMENT: Single dose/42-day follow-up.

OBJECTIVE(S): To assess that the G4-reassortant rotavirus vaccine is generally safe and well tolerated, in order to include it in a multivalent oral live rotavirus vaccine.

STUDY DESIGN: Double-blinded, placebo-controlled randomized study organized in 2 stages. Stage 1 was conducted in healthy adults; Stage 2 was conducted in healthy infants, after subjects from Stage 1 had been followed 14 days without any vaccine-related serious adverse experiences. Within each stage, subjects were randomized between vaccine and placebo groups at a ratio of 2:1.

SUBJECT ACCOUNTING:

	Adults (Age Range in Years)			Infants (Age Range in Weeks)		
	Rotavirus (G4 Vaccine)	Placebo	Total	Rotavirus (G4 Vaccine) Vaccine	Placebo	Total
ENTERED: Total	10	5	15	47	23	70
Male (age range)	6 (26 to 53)	3 (23 to 30)	9 (23 to 53)	25 (8 to 21)	13 (9 to 21)	38 (8 to 21)
Female (age range)	4 (27 to 54)	2 (28 to 32)	6 (27 to 54)	22 (9 to 21)	10 (8 to 21)	32 (8 to 21)
COMPLETED:	10	5	15	46	22	68
DISCONTINUED: Total	0	0	0	1	1	2
Clinical adverse experience	0	0	0	0	0	0
Deviation from protocol	0	0	0	0	0	0
Refused further participation	0	0	0	0	0	0
Lost to follow-up	0	0	0	1	1	2

DOSAGE/FORMULATION NOS.:

Regimen: A single, 1-mL dose of clinical material, vaccine or placebo, was administered orally to each subject on Day 0. The vaccine was given approximately one-half hour after the administration of a buffering agent.

Clinical Trial Material: The vaccine contained G4 human-bovine reassortant rotavirus with an estimated final titer of 10^7 plaque-forming units (PFU) in a 1-mL dose. The vaccine composition included (b) (4) Medium (b) (4) at (b) (4) at (b) (4) at (b) (4) and sucrose (b) (4), Lot No. V260-OSO-001-D001. Trace components of fetal bovine serum may also have been present in the vaccine. The placebo was composed of (b) (4) Medium (b) (4) at (b) (4) at (b) (4), and Sucrose (b) (4), Lot No. 1506/W-D151.

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CSR SYNOPSIS (CONT.)
Protocol 005

V260
Live Pentavalent Human-Bovine
Rotavirus Reassortant Vaccine
Oral; Rotavirus Gastroenteritis

SUBJECT ACCOUNTING:

	Rotavirus (G1, G2, G3, G4, and P1) Vaccine			Group 4 Rotavirus (G1, G2, G3, G4) Vaccine	Group 5 Rotavirus (P1) Vaccine	
	Group 1 $5x10^6$ PFU/ Reassortant	Group 2 $1.6x10^6$ PFU/ Reassortant	Group 3 $5x10^5$ PFU/ Reassortant	$5x10^6$ PFU/ Reassortant	$5x10^6$ PFU/ Reassortant	Group 6 Placebo
Entered:	375	328	324	270	327	322
Male (age range – months)	201 (2 to 8)	179 (2 to 8)	156 (2 to 8)	134 (2 to 8)	165 (2 to 8)	152 (2 to 8)
Female (age range – months)	174 (2 to 8)	149 (2 to 8)	168 (1 to 9)	136 (2 to 8)	162 (2 to 8)	170 (2 to 8)
Vaccinated At:						
Vaccination Visit 1:	375	328	324	270	327	322
Vaccination Visit 2:	358	305	315	256	317	307
Vaccination Visit 3:	349	299	307	251	310	297
Completed First Season:	348	295	306	248	307	296
Discontinued:	27	33	18	22	20	26
Clinical adverse experience	0	0	0	0	0	0
Deviation from protocol	0	0	0	0	0	0
Refused further participation	12	13	12	7	6	3
Lost to follow-up	1	4	1	3	2	1
Clinical adverse experience – discontinued test vaccine	14	16	5	12	12	22

DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each dose was 1.0 mL of vaccine (high-dose, middle-dose, or low-dose pentavalent; quadrivalent; or monovalent) or placebo. Dose 1 was administered on Day 0, Dose 2 was administered 4 to 8 weeks after Dose 1, and Dose 3 was administered 4 to 8 weeks after Dose 2.

Clinical Material:

Group 1: G1, G2, G3, G4, and P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of $5x10^6$ plaque-forming units (PFU)/reassortant, Lot No. V260 OSO 003 E001.

Group 2: G1, G2, G3, G4, and P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of $1.6x10^6$ PFU/reassortant, Lot No. V260 OSO 003 C001.

Group 3: G1, G2, G3, G4, and P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of $5x10^5$ PFU/reassortant, Lot No. V260 OSO 003 B001.

Group 4: G1, G2, G3, and G4 serotype of human-bovine rotavirus reassortants, with an estimated final titer of $5x10^6$ PFU/reassortant, Lot No. V260 OSO 002 C001.

Group 5: P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of $5x10^6$ PFU/reassortant, Lot No. V260 OSO 004 E001

Group 6: Contained no human-bovine rotavirus reassortants, Lot No. PV260 OSO 02 A001.

All Groups (including placebo) contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4) and sucrose (b) (4) (b) (4) The vaccine groups (Groups 1 to 5) contained (b) (4) at (b) (4) and may have contained trace components of fetal bovine serum. All Groups (including placebo) were packaged in code-labeled, single-dose vials stored at (b) (4)

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DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each vaccination was 2.0 mL of vaccine or placebo. Vaccination 1 was to be administered on Day 1, Vaccination 2 was to be administered 28 to 70 days after Vaccination 1, and Vaccination 3 was to be administered 28 to 70 days after Vaccination 2.

Clinical Material: RotaTeq™ at expiry potency (Lot Nos. V260 VAO 019Q001 and V260 VAO 019Q002) contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate-80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final aggregate potency of ~1.1 x 10^7 infectious units (IU)/dose in approximately 2.0 mL of buffer/stabilizer. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) µg/dose. Trace components of fetal bovine serum may have also been present.

The placebo (Lot No. PV260 VAO 009A009) was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, and no greater than (b) (4) mg of polysorbate-80.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA:

Efficacy: The case definition for rotavirus gastroenteritis required subjects to meet both of the following criteria: (1) 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) Rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms. All rotavirus-positive stools were evaluated for serotype identification by polymerase chain reaction (PCR). Only naturally-occurring rotavirus AGEs caused by the human rotavirus G- serotypes in the vaccine were included in the primary analysis.

Immunogenicity: In a subset of approximately 175 subjects, antibody responses to the vaccine were evaluated by several assays. Serum samples were collected before Dose 1 and approximately 42 days after Dose 3. Serum was tested by modified enzyme-linked immunosorbent assay (ELISA) for serum neutralizing antibodies (SNA) against the rotavirus serotypes contained within the vaccine (G1, G2, G3, G4, P1, and WC3 (the WC3 serotype is also characterized as G6 and P7[5] throughout this document)). Serum anti-rotavirus IgA was also evaluated.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and/or diarrhea.

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CSR SYNOPSIS (CONT.)
Protocol 009

V260
Rotavirus Vaccine, Live, Oral, Pentavalent

-2-

DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were to be administered to each subject orally. The volume of each vaccination was approximately 2.0 mL of vaccine or placebo. Vaccination 1 was administered on Day 1, Vaccination 2 was to be administered 28 to 70 days after Vaccination 1, and Vaccination 3 was to be administered 28 to 70 days after Vaccination 2.

Clinical Material: RotaTeq™ (Lot 1 No.: V260 VAO 020 R001; Lot 2 No.: V260 VAO 020 R002; and Lot 3 No.: V260 VAO 020 R003) was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate 80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 in approximately 2.0 mL of buffer/stabilizer with a measured aggregate potency of 8.81 X 10^7 Infectious Units (IU)/dose, 8.01 X 10^7 IU/dose, and 6.91 X 10^7 IU/dose for Lot 1, Lot 2, and Lot 3, respectively.

The placebo (Lot No. PV260 VAO 022 P001) was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate 80.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA:

Immunogenicity: Antibody responses (SNA Postdose 3 GMTs against rotavirus serotypes G1, G2, G3, G4, and P1 and serum anti-rotavirus IgA) to RotaTeq™/placebo were evaluated in all subjects. These assays were performed on one serum sample collected from each subject approximately 42 days Postdose 3. In addition, Predose 1 serum samples were to be collected in a subset of approximately 140 subjects (approximately 40 subjects per vaccine lot and approximately 20 subjects in the placebo group) at predetermined study sites. Predose 1 serum samples were assayed for SNA against rotavirus serotypes G1, G2, G3, G4, and P1.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and diarrhea.

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Product: V260
Protocol/Amendment No.: 006-00 37

E. STUDY DESIGN (CONT.)

Each container will be labeled with double-panel tear-off labels containing the following: unique vial identification number, packing identification number, rotavirus vaccine or placebo, protocol (006) V260, fill volume, dosing instructions (follow protocol for dosing instructions/for oral route only), and storage conditions. The tear-off portion of the label will also contain the unique vial identification number and a space for transcribing the dose number and the allocation number assigned to the patient by the IVRS. This tear-off label will be affixed to the L-page in the subject workbooklet.

All clinical material (i.e., vaccine and placebo) must be accounted for by appropriately documenting the administration (or wasting) of each vial. Empty or partially empty vials and vials that have been thawed but not used must be disposed of accordingly to standard methods for handling medical infectious hazardous waste.

A sample label will be similar to the following:

MERCK RESEARCH LABORATORIES
XXXXXX WP-XXXX SUBJECT NO. DOSE NO.
ROTAVIRUS VACCINE/PLACEBO ORAL SOLUTION
2.0ML DOSE ADMINISTER PER PROTOCOL 006 (V260)
S##### STORE REFRIGERATED(2-8°C)
KLIINISEEN TUTKIMUKSEEN/FOR KLINISK PROVNING
Caution: New Drug Limited by Federal (U.S.A.) Law to Investigational Use

1) Description of the Vaccine to be Administered

Vaccine administered to Group 1 contains human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final titer of (b) (4) (b) (4) in a 2.0-mL dose. A vaccine dose contains approximately (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. (b) (4) (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

2) Description of the Placebo

Placebo administered to Group 2 is a 2.0-mL dose that contains approximately (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80.

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Product: V260
Protocol/Amendment No.: 006-01 52

E. STUDY DESIGN (CONT.)

A sample label will be similar to the following:

MERCK RESEARCH LABORATORIES # XXXXXX WP-XXXX SUBJECT NO. DOSE NO. ROTAVIRUS VACCINE/PLACEBO ORAL SOLUTION 2.0ML DOSE ADMINISTER PER PROTOCOL 006 (V260) S##### STORE REFRIGERATED(2-8˚C) KLIINISEEN TUTKIMUKSEEN/FOR KLINISK PROVNING Caution: New Drug Limited by Federal (U.S.A.) Law to Investigational Use

Additional country-specific label requirements will be used on the vaccine/placebo vial box for clinical use as required in other individual countries.

Concomitant use vaccine vials will receive a single panel, open label including at least the following information: product, lot number, expiration date, packaging control number, applicable storage conditions, and dosing information. PREVNAR™ is in short supply at the time of writing this protocol. If it is not available for Merck & Co., Inc. to supply, the subset of subjects in the U.S. concomitant use portion of the study may still receive PREVNAR™ provided by their local physician. The lot number of the vial will be documented on the appropriate worksheet. Note: If PREVNAR™ is provided locally by the physician, the single panel, open label will not be used on PREVNAR™.

e. Description of Clinical Material to be Administered

Description of RotaTeq™, the Study Vaccine to be Administered

RotaTeq™, which will be administered to Group 1, contains human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final dose of (b) (4) in a 2.0-mL dose. A vaccine dose contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

Description of the Placebo: Placebo, which will be administered to Group 2, is a 2.0-mL dose that contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80.

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Product: V260
Protocol/Amendment No.: 006-02 47

E. STUDY DESIGN (CONT.)

A sample label will be similar to the following:

MERCK RESEARCH LABORATORIES # XXXXXX WP-XXXX SUBJECT NO. DOSE NO. ROTAVIRUS VACCINE/PLACEBO ORAL SOLUTION 2.0ML DOSE ADMINISTER PER PROTOCOL 006 (V260) S##### STORE REFRIGERATED(2-8°C) KLIINISEEN TUTKIMUKSEEN/FOR KLINISK PROVNING Caution: New Drug Limited by Federal (U.S.A.) Law to Investigational Use

Additional country-specific label requirements will be used on the vaccine/placebo vial box for clinical use as required in other individual countries.

Concomitant use vaccine vials will receive a single panel, open label including at least the following information: product, lot number, expiration date, packaging control number, applicable storage conditions, and dosing information. PREVNAR™ is in short supply at the time of writing this protocol. If it is not available for Merck & Co., Inc. to supply, the subset of subjects in the U.S. concomitant use portion of the study may still receive PREVNAR™ provided by their local physician. The lot number of the vial will be documented on the appropriate worksheet. Note: If PREVNAR™ is provided locally by the physician, the single panel, open label will not be used on PREVNAR™.

e. Description of Clinical Material to be Administered

Description of RotaTeq™, the Study Vaccine to be Administered

RotaTeq™, which will be administered to Group 1, contains human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final dose of (b) (4) in a 2.0-mL dose. A vaccine dose contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

Description of the Placebo: Placebo, which will be administered to Group 2, is a 2.0-mL dose that contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80.

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Product: V260
Protocol/Amendment No.: 006-03 60

E. STUDY DESIGN (CONT.)

Additional country-specific label requirements will be used on the vaccine/placebo dose package box for clinical use as required in other individual countries.

g. Description of Clinical Material to be Administered

Description of RotaTeq™, the Study Vaccine to be Administered

RotaTeq™, which will be administered to Group 1, contains human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final dose of (b) (4) in a 2.0-mL dose. A vaccine dose contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no > (b) (4) mg polysorbate 80. (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

Description of the Placebo: Placebo, which will be administered to Group 2, is a 2.0-mL dose that contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) tissue culture medium, and no > (b) (4) mg polysorbate 80.

Other Childhood Vaccines to be Administered Concomitantly With RotaTeq™ in the Subset of Subjects in the U.S. Efficacy Portion of the Study

U.S. Concomitant Efficacy Sites:

COMVAX™: (*Haemophilus* b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B[Recombinant] Vaccine): Each 0.5-mL dose contains 7.5 mcg of purified capsular polysaccharide (PRP) of *Haemophilus* b (Hib) (b) (4) 125 mcg of outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B and 5.0 mcg of hepatitis B surface antigen (HBsAg). Each dose contains 225 mcg aluminum as (b) (4), and 35 mcg of sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride. The vaccine contains (b) (4). The vaccine is supplied in 0.5-mL single dose vials.

Included in each shipment of COMVAX™ will be a (b) (4) (b) (4)

Prior to receiving a shipment, site personnel should review the *Instructions to Site* and contact the Medical Program Coordinator (MPC) with any questions.

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A sample label will be similar to the following:

MERCK RESEARCH LABORATORIES
XXXXXX WP-XXXX SUBJECT NO. DOSE NO.
ROTAVIRUS VACCINE/PLACEBO ORAL SOLUTION
2 ML DOSE ADMINISTER PER PROTOCOL 006 (V260)
S##### STORE REFRIGERATED(2-8°C)
KLIINISEEN TUTKIMUKSEEN/FOR KLINISK PROVNING
Caution: New Drug Limited by Federal (U.S.A.) Law to Investigational Use

Additional country-specific label requirements may be used on the vaccine/placebo vial or dose package box for clinical use as required in other individual countries.

U.S. Concomitant Use

Concomitant use vaccine vials will be labeled with a single panel, open label including at least the following information: product, lot number, expiration date, packaging control number, applicable storage conditions, and dosing information. PREVNAR™ has been in short supply over the course of the study. If it is not available for Merck & Co., Inc. to supply, the subset of subjects in the U.S. concomitant use portion of the study may still receive PREVNAR™ provided by their local physician. The lot number and expiration date of the vial will be documented on the appropriate worksheet. Note: If PREVNAR™ is provided locally by the physician, the single panel, open label will not be used on PREVNAR™.

f. Description of Clinical Material to be Administered

Description of RotaTeq™, the Study Vaccine to be Administered

RotaTeq™, which will be administered to Group 1, contains human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final dose **range of 6.5 x 10^7 IU to 1.2 x 10^8 IU** in an approximate 2-mL dose. RotaTeq™ is a buffered, liquid product that is stored at 4°C, and will be marketed in a plastic container designed for direct oral delivery. A vaccine dose contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) -mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. (b) (4) (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

Description of the Placebo: Placebo, which will be administered to Group 2, is approximately a 2-mL dose that contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) -mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80.

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Reference P007

Study of the Efficacy, Safety, and Immunogenicity of RotaTeq™ at Expiry Potency

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CLINICAL STUDY REPORT

Study of the Efficacy, Safety, and Immunogenicity of RotaTeq™ at Expiry Potency

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DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each vaccination was 2.0 mL of vaccine or placebo. Vaccination 1 was to be administered on Day 1, Vaccination 2 was to be administered 28 to 70 days after Vaccination 1, and Vaccination 3 was to be administered 28 to 70 days after Vaccination 2.

Clinical Material: RotaTeq™ at expiry potency (Lot Nos. V260 VAO 019Q001 and V260 VAO 019Q002) contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate-80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final aggregate potency of ~1.1 x 10^7 infectious units (IU)/dose in approximately 2.0 mL of buffer/stabilizer. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) µg/dose. Trace components of fetal bovine serum may have also been present.

The placebo (Lot No. PV260 VAO 009A009) was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, and no greater than (b) (4) mg of polysorbate-80.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA:

Efficacy: The case definition for rotavirus gastroenteritis required subjects to meet both of the following criteria: (1) 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) Rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms. All rotavirus-positive stools were evaluated for serotype identification by polymerase chain reaction (PCR). Only naturally-occurring rotavirus AGEs caused by the human rotavirus G- serotypes in the vaccine were included in the primary analysis.

Immunogenicity: In a subset of approximately 175 subjects, antibody responses to the vaccine were evaluated by several assays. Serum samples were collected before Dose 1 and approximately 42 days after Dose 3. Serum was tested by modified enzyme-linked immunosorbent assay (ELISA) for serum neutralizing antibodies (SNA) against the rotavirus serotypes contained within the vaccine (G1, G2, G3, G4, P1, and WC3 (the WC3 serotype is also characterized as G6 and P7[5] throughout this document)). Serum anti-rotavirus IgA was also evaluated.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and/or diarrhea.

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5.4.2 Identity of Clinical Supplies

5.4.2.1 RotaTeq™ at Expiry Potency and Placebo

Each dose of RotaTeq™ at expiry potency contained human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final aggregate potency of ~1.1 x10^7 infectious units (IU)/dose in approximately 2.0 mL of buffer/stabilizer. The potencies of the individual human-bovine reassortants were determined via the Multivalent Quantitative Polymerase Chain Reaction Assay (M-QPA). A description of this assay can be found in Section II.11.6. The vaccine was a buffered, liquid product that was ideally stored at 2 to 8°C. The formulation used in this study, when fully characterized, contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate-80. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) µg/dose. Trace components of fetal bovine serum may have also been present. The stability of vaccine was assessed at predefined evaluation points throughout the study.

The placebo was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, and no greater than (b) (4) mg of polysorbate-80.

Vaccine was provided in kits. Each kit was intended for a single subject and contained 3 doses of vaccine/placebo. The kits were labeled with at least the following information: Rotavirus Vaccine/Placebo, 3 vials each containing 2.0-mL dose for oral administration, store at 2 to 8°C, AN, protocol number, packaging control number (WP-XXXX (control number pertained to shipments that included both vaccine and placebo)), SPONSOR name and address, and applicable caution statements and any additional country-specific label requirements.

Two (2) mL of vaccine or placebo were drawn up from the vial using a syringe. The needle was removed from the syringe and the vaccine was dispensed orally to the infant.

Once labeled, RotaTeq™ at expiry potency was indistinguishable from the placebo. Thus, upon arrival at the clinical study site, the treatment contained within each vial was blinded to the investigator, the subject, and the parent/legal guardian.

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V260
Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine for Oral Administration

CLINICAL STUDY REPORT
I. SYNOPSIS

Quadrivalent Vaccine Containing Serotypes G1, G2, G3, and P1

PROTOCOL TITLE/NO.: Safety, Tolerability, and Immunogenicity of Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine in Healthy Adults — #001

INVESTIGATOR(S)/STUDY CENTER(S): Paul A. Offit, M.D., Philadelphia, PA, U.S.A.

PRIMARY THERAPY PERIOD: 19-Jun-1993 to 08-Jul-1993; Clinical Data Cutoff Date: 04-Dec-1996; Serology Cutoff Date: 11-Nov-1996; Study Completion Date: 08-Jul-1993.

CLINICAL PHASE: I

DURATION OF TREATMENT: Single dose/14-day follow-up.

OBJECTIVE(S): Primary Objective: To determine if the vaccine is safe in healthy immune adults. Secondary Objective: To investigate immune responses after a single dose of quadrivalent vaccine when administered orally to healthy adults.

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial.

SUBJECT ACCOUNTING:

	Rotavirus Vaccine	Placebo
ENTERED: Total	20	11
Male (age range-years)	10 (22 to 40)	5 (21 to 42)
Female (age range-years)	10 (19 to 47)	6 (22 to 34)
COMPLETED:	19	11
DISCONTINUED: Total	1	0
Clinical adverse experience	0	0
Laboratory adverse experiences	0	0
Refused further participation	1	0

DOSAGE/FORMULATION NOS.: Regimen: A 1.0-mL dose of vaccine/placebo orally administered, following an 8-hour overnight fast. One-half hour before administration, subjects were given 4 teaspoons of MAALOX™ (magnesia alumina oral suspension antacid, Novartis Consumer Health, Inc.) to ensure uniform gastric buffering and were asked to refrain from eating for 1 hour after administration of vaccine/placebo. Clinical Material: Quadrivalent human-bovine rotavirus reassortant vaccine, Lot 1340A/C-Y560A, 1.2-mL vial. This vaccine contained serotypes G1, G2, G3, and P1 each with an estimated final titer of 1 x 10^7 plaque-forming units (PFU)/mL in (b) (4) Medium (b) (4) (b) (4) with (b) (4) at (b) (4) at (b) (4), and (b) (4) at (b) (4). Placebo, Lot 1341/C-Y561, 1.2-mL vial. This placebo contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4)

DIAGNOSIS/INCLUSION CRITERIA: Healthy adults 18 years of age or older who had no: known hypersensitivity to any component of the rotavirus vaccine, e.g., (b) (4); known or suspected impairment of immunologic function; fever, ≥100°F (oral) at the time of immunization; clinical evidence of chronic or active gastrointestinal illness prior to immunization; other vaccines given within 14 days prior to administration of study vaccine; history of drug or alcohol abuse. Subjects were not pregnant or expecting to conceive during the study period. Subjects must have agreed to use an acceptable method of birth control for 2 weeks after the immunization. Abstinence was considered an acceptable method of birth control. Subjects did not have any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA: Immunogenicity Evaluation: Serum neutralizing antibody levels (for each of G1, G2, G3, P1, bovine WC3 strain, and human W179 strain specificities). Safety Evaluation: Incidence of serious vaccine-related adverse experiences (Days 0 to 14 postvaccination); fecal vaccine virus shedding (Days 2 to 7 postvaccination); temperature elevations (Days 0 to 14 postvaccination); and serum alanine transaminase (ALT) levels (Days 0 and 14 postvaccination).

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CSR SYNOPSIS (CONT.)
Protocol 002

V260
Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine.
Oral Rotavirus Gastroenteritis

DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each dose was 1.0 mL of quadrivalent G1, G2, G3, and P1 human-bovine reassortant rotavirus vaccine or placebo. Dose 1 was given on Day 0, Dose 2 was given 6 to 8 weeks after Dose 1, and Dose 3 was given 6 to 8 weeks after Dose 2.

Clinical Trial Material: G1, G2, G3, and P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of 4 X 10^7 plaque-forming units (PFU), Lot No. 1340A/C-Y560A. Placebo represented buffer alone; i.e., without quadrivalent human-bovine rotavirus reassortants, Lot No. 1341/C-Y561. Vaccine and placebo contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4). Trace components of fetal bovine serum and (b) (4) saline may have been present in the vaccine and placebo.

CLINICAL MATERIAL:

Vaccine	Lot Number-Fill Number	Dosage	Potency (PFU/dose)	Package
Live rotavirus vaccine	1340A/C-Y560A	1.0 mL	4 x 10^7	Code-labeled vial kept at (b) (4)
Placebo	1341/C-Y561	1.0 mL	0	Code-labeled vial kept at (b) (4)

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 2 to 6 months of age who had no known or suspected impairment of immunologic function; no prior administration of any rotavirus vaccine; no fever (defined as a rectal temperature of ≥100.4°F) at the time of immunization; no history of chronic diarrhea or failure to thrive; no clinical evidence of active gastrointestinal disease; no other vaccines given within (+/-) 14 days of any dose of vaccine; no condition that, in the opinion of the investigator, could have interfered with the evaluation of the study objectives; and no infant who resided in a household with an immunocompromised individual.

EVALUATION CRITERIA: **Efficacy:** The case definition for rotavirus gastroenteritis was that a subject must have met both of the following criteria: (1) ≥3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting. (2) Rotavirus must have been identified in a stool specimen taken within 14 days of the onset of symptoms. **Immunogenicity:** Serum samples, taken Predose 1 and Postdose 3, were tested by enzyme immunoassay (EIA) for serum neutralizing antibody (SNA) against G1, G2, G3, P1a, P1G1, G6, and P7. Serum was also tested for anti-rotavirus IgA and IgG. Stool samples, taken Predose 1 and Postdose 3, were tested for fecal anti-rotavirus IgA and total fecal IgA, as well as for fecal neutralizing antibody (FNA) against G1, G6, P1a, and P7. **Safety:** The subjects' parents/guardians were asked to record any adverse experiences that occurred within 14 days after any vaccination. Temperatures were recorded daily for 7 days after each administration of vaccine/placebo. Stool samples for viral shedding were obtained from all participants between Day 3 and Day 5 after Dose 1. In addition, the Philadelphia study site collected stool samples for vaccine viral shedding 1 to 2, 3 to 5, 7 to 9, and ~15 days following each dose.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The primary efficacy hypothesis that the quadrivalent rotavirus vaccine provides efficacy against rotavirus disease throughout one rotavirus season was tested using an exact conditional procedure. The primary hypothesis in the protocol refers to 80% efficacy, which is the expected efficacy that was used for power and sample size calculations; however, the primary hypothesis was tested for vaccine efficacy >0.0% relative to placebo, as noted in the Data Analysis Plan (DAP). A point estimate and exact two-sided 95% confidence interval for vaccine efficacy were also calculated. In order for the quadrivalent rotavirus vaccine to be declared efficacious (i.e., in order to reject the null hypothesis), the lower bound on the confidence interval for vaccine efficacy had to exceed 0%. If there were 160 evaluable infants per group, and assuming that the true incidence of disease in the placebo group would be 10% and that the vaccine would be 80% efficacious in the prevention of rotavirus disease, there would be 80% power to reject the primary null hypothesis. One hundred eighty (180) evaluable infants per group would provide 80% power with an attack rate as low as 9% in the placebo group.

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CSR SYNOPSIS (CONT.)
Protocol 003

V260
G1 G2 Reassortant Rotavirus
Vaccine Live (Human-Bovine)
Oral
Rotavirus Gastroenteritis

-2-

SUBJECT ACCOUNTING:

	Rotavirus (G1, G2) Vaccine				Placebo (Groups 2, 4, 6, and 8 Combined)
	1.0 mL – No Buffer (Group 1)	1.0 mL – 1x Buffer (Group 3)	2.5 mL – 1x Buffer (Group 5)	1.0 mL – Conc. Buffer (Group 7)	
ENTERED: Total	142	150	147	142	150
Male (age range—weeks)	64 (8 to 21)	74 (8 to 21)	76 (6 to 21)	77 (8 to 21)	79 (8 to 21)
Female (age range—weeks)	78 (6 to 21)	76 (8 to 21)	71 (7 to 21)	65 (8 to 21)	71 (8 to 21)
COMPLETED:	136	138	137	132	138
DISCONTINUED: Total	6	12	10	10	12
Clinical adverse experience	0	1	0	2	2
Refused further participation	3	6	6	5	6
Lost to follow-up	3	5	4	3	4

DOSAGE/FORMULATION NOS.: Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of administration was either 1.0 mL or 2.5 mL, depending upon the subject's group assignment. Each dose was provided under the following schedule:
Dose 1, given on Day 0.
Dose 2, given between Days 42 and 56.
Dose 3, given between Days 84 and 98.

Group	Prefeeding	Vaccine Vol (mL)	Buffer/Stabilizer	PFU/Dose
1	Yes	1.0	None	1x 10^7 PFU
2†	Yes	1.0	None	0
3	No	1.0	1x	1x 10^7 PFU
4†	No	1.0	1x	0
5	No	2.5	1x	1x 10^7 PFU
6†	No	2.5	1x	0
7	No	1.0	Concentrate	1x 10^7 PFU
8†	No	1.0	Concentrate	0

† Placebo.

CLINICAL MATERIAL: G1 and G2 human-bovine reassortant rotavirus vaccine, a live virus vaccine, Lots No. 1507/W-D152, 1493/W-C971, 1494/W-C972, and 1495/W-C973. The vaccine contained serotypes G1 and G2, each with an estimated final titer of 5 x 10^6 PFU/reassortant or a total of 1x10^7 PFU G1 and G2 human-bovine rotavirus reassortant vaccine per dose, in (b) (4) Medium (b) (4) (b) (4). Placebo represented buffer alone; i.e., without rotavirus vaccine, Lots No. 1506/W-D151, 1489/W-C967, 1490/W-C968, and 1491/W-C969.

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MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

V260
G4 Human-Bovine Reassortant
Rotavirus Vaccine, Oral
Rotavirus gastroenteritis

PROTOCOL TITLE/NO.: Safety and Tolerability of Oral, Live G4 Human-Bovine Reassortant Rotavirus Vaccine in Healthy Adults and Healthy Infants #004

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (02) U.S.

PRIMARY THERAPY PERIOD: 19-Mar-1998 to 07-Jul-1998 (last dose of therapy).
Study completed: 18-Aug-1998.
Clinical Case Report Form and Laboratory Data In-House Cut-off Date: 10-Sep-1999.

CLINICAL PHASE: IIb

DURATION OF TREATMENT: Single dose/42-day follow-up.

OBJECTIVE(S): To assess that the G4-reassortant rotavirus vaccine is generally safe and well tolerated, in order to include it in a multivalent oral live rotavirus vaccine.

STUDY DESIGN: Double-blinded, placebo-controlled randomized study organized in 2 stages. Stage 1 was conducted in healthy adults; Stage 2 was conducted in healthy infants, after subjects from Stage 1 had been followed 14 days without any vaccine-related serious adverse experiences. Within each stage, subjects were randomized between vaccine and placebo groups at a ratio of 2:1.

SUBJECT ACCOUNTING:

	Adults (Age Range in Years)			Infants (Age Range in Weeks)		
	Rotavirus (G4 Vaccine)	Placebo	Total	Rotavirus (G4 Vaccine) Vaccine	Placebo	Total
ENTERED: Total	10	5	15	47	23	70
Male (age range)	6 (26 to 53)	3 (23 to 30)	9 (23 to 53)	25 (8 to 21)	13 (9 to 21)	38 (8 to 21)
Female (age range)	4 (27 to 54)	2 (28 to 32)	6 (27 to 54)	22 (9 to 21)	10 (8 to 21)	32 (8 to 21)
COMPLETED:	10	5	15	46	22	68
DISCONTINUED: Total	0	0	0	1	1	2
Clinical adverse experience	0	0	0	0	0	0
Deviation from protocol	0	0	0	0	0	0
Refused further participation	0	0	0	0	0	0
Lost to follow-up	0	0	0	1	1	2

DOSAGE/FORMULATION NOS.:

Regimen: A single, 1-mL dose of clinical material, vaccine or placebo, was administered orally to each subject on Day 0. The vaccine was given approximately one-half hour after the administration of a buffering agent.

Clinical Trial Material: The vaccine contained G4 human-bovine reassortant rotavirus with an estimated final titer of 10^7 plaque-forming units (PFU) in a 1-mL dose. The vaccine composition included (b) (4) Medium (b) (4) at (b) (4) at (b) (4) at (b) (4), and sucrose (b) (4), Lot No. V260-OSO-001-D001. Trace components of fetal bovine serum may also have been present in the vaccine. The placebo was composed of (b) (4) Medium (b) (4) at (b) (4) at (b) (4) and Sucrose (b) (4), Lot No. 1506/W-D151.

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E. STUDY DESIGN (CONT.)

If immediately following any dose of RotaTeq™/placebo, a subject develops a SAE that is judged by the investigator to be related to vaccination, the subject should not receive any additional doses; however, they should continue to be followed for safety.

A masked allocation schedule will be provided to a pre-designated Merck clinical monitor, a pre-designated Merck subsidiary personnel and a pre-designated CRO personnel. This masked allocation schedule should be used ONLY if unblinding is approved by the Merck clinical monitor and is absolutely essential for the welfare of the subject. It is also important to remember that for potential cases of intussusception, it is desirable to remain blinded to the treatment arm given that intussusception is the primary safety endpoint of another concurrently enrolling study, which is being monitored by a DSMB.

Description of RotaTeq™ and Placebo: Both RotaTeq™ and the placebo contain ~2 mL of a buffered liquid consisting of (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. RotaTeq™ also contains human-bovine reassortants G1, G2, G3, G4, and P1 with an estimated final dose of 1.0×10^7 total Infectious Units[2], and (b) (4). Trace amounts of fetal bovine serum may also be present.

b. Special Handling Requirements

Vials of RotaTeq™ and placebo will be shipped to the study sites frozen on dry ice. The vaccine and placebo will be indistinguishable, with ~2.5 mL of material in a 6 mL vial. The RotaTeq™/placebo should be placed in the refrigerator at (b) (4) to 8°C immediately after arrival, and should be stored refrigerated until needed for administration. A refrigerator temperature log must be maintained at the site. The log will be reviewed throughout the course of the study by the site field monitors. Refrigerator temperatures of (b) (4) to 8°C are acceptable for storage of RotaTeq™/placebo. If the refrigerator temperature moves outside of this range (b) (4) or above 8°C [46.4°F]), the SPONSOR should be notified and the vaccine should not be used.

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[2] Infectious units are used to designate the potency values generated in the novel M-QPA potency assay. The assay enumerates the accumulation of viral nucleic acid following a productive infection and relates it to a reference standard of known potency. This is a Merck & Co., Inc. specific assay.

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Product: V260
Protocol/Amendment No.: 007-01 26

E. STUDY DESIGN (CONT.)

A masked allocation schedule will be provided to a predesignated Merck clinical monitor, a predesignated Merck subsidiary personnel and a predesignated CRO personnel. This masked allocation schedule should be used ONLY if unblinding is approved by the Merck clinical monitor and is absolutely essential for the welfare of the subject. It is also important to remember that for potential cases of intussusception, it is desirable to remain blinded to the treatment arm given that intussusception is the primary safety endpoint of another concurrently enrolling study, which is being monitored by a DSMB.

Description of RotaTeq™ and Placebo: Both RotaTeq™ and the placebo contain ~2 mL of a buffered liquid consisting of (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. RotaTeq™ also contains human-bovine reassortants G1, G2, G3, G4, and P1 with an estimated final dose of 1.0 x 10^7 total Infectious Units, and (b) (4). Trace amounts of fetal bovine serum may also be present.

b. Special Handling Requirements

Vials of RotaTeq™ and placebo will be shipped to the study sites frozen on dry ice. The vaccine and placebo will be indistinguishable, with ~2.5 mL of material in a 6 mL vial. The RotaTeq™/placebo should be placed in the refrigerator at (b) (4) to 8°C immediately after arrival, and should be stored refrigerated until needed for administration. A refrigerator temperature log must be maintained at the site. The log will be reviewed throughout the course of the study by the site field monitors. Refrigerator temperatures of (b) (4) to 8°C are acceptable for storage of RotaTeq™/placebo. If the refrigerator temperature moves outside of this range (b) (4) or above 8°C [46.4°F]), the SPONSOR should be notified and the vaccine should not be used.

If a vial is needed for administration and is still frozen, it should be thawed by letting it stand at room temperature for 30 minutes. Thawing may be initiated by warming with gloved hands; however, it is recommended that hand warming end when thawing approaches completion and a small amount of frozen material is still visible. RotaTeq™/placebo should be administered within 30 minutes of thawing. In the event a vial has been mishandled and cannot be used (e.g., it is not given within 30 minutes of thawing), study personnel should contact the appropriate MPC.

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E. STUDY DESIGN (CONT.)

A masked allocation schedule will be provided to a predesignated Merck clinical monitor, a predesignated Merck subsidiary personnel and a predesignated CRO personnel. This masked allocation schedule should be used ONLY if unblinding is approved by the Merck clinical monitor and is absolutely essential for the welfare of the subject. It is also important to remember that for potential cases of intussusception, it is desirable to remain blinded to the treatment arm given that intussusception is the primary safety endpoint of another concurrently enrolling study, which is being monitored by a DSMB.

Description of RotaTeq™ and Placebo: Both RotaTeq™ and the placebo contain ~2 mL of a buffered liquid consisting of (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. RotaTeq™ also contains human-bovine reassortants G1, G2, G3, G4, and P1 with an estimated final dose of 1.0 x 10^7 total Infectious Units, and (b) (4). Trace amounts of fetal bovine serum may also be present.

b. Special Handling Requirements

Vials of RotaTeq™ and placebo will be shipped to the study sites frozen on dry ice. The vaccine and placebo will be indistinguishable, with ~2.5 mL of material in a 6 mL vial. The RotaTeq™/placebo should be placed in the refrigerator at (b) (4) to 8°C immediately after arrival, and should be stored refrigerated until needed for administration. A refrigerator temperature log must be maintained at the site. The log will be reviewed throughout the course of the study by the site field monitors. Refrigerator temperatures of (b) (4) to 8°C are acceptable for storage of RotaTeq™/placebo. If the refrigerator temperature moves outside of this range (b) (4) or above 8°C [46.4°F]), the SPONSOR should be notified and the vaccine should not be used.

If a vial is needed for administration and is still frozen, it should be thawed by letting it stand at room temperature for 30 minutes. Thawing may be initiated by warming with gloved hands; however, it is recommended that hand warming end when thawing approaches completion and a small amount of frozen material is still visible. RotaTeq™/placebo should be administered within 30 minutes of thawing. In the event a vial has been mishandled and cannot be used (e.g., it is not given within 30 minutes of thawing), study personnel should contact the appropriate MPC.

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Reference P009

MRL Clinical Study Report, Multicenter Study: Comparison of the Immunogenicity and Safety of Three Consistency Lots of RotaTeq™ in Healthy Infants (Protocol 009)

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CLINICAL STUDY REPORT

Comparison of the Immunogenicity and Safety of Three Consistency Lots of RotaTeq™ in Healthy Infants (Protocol 009)

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DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were to be administered to each subject orally. The volume of each vaccination was approximately 2.0 mL of vaccine or placebo. Vaccination 1 was administered on Day 1, Vaccination 2 was to be administered 28 to 70 days after Vaccination 1, and Vaccination 3 was to be administered 28 to 70 days after Vaccination 2.

Clinical Material: RotaTeq™ (Lot 1 No.: V260 VAO 020 R001; Lot 2 No.: V260 VAO 020 R002; and Lot 3 No.: V260 VAO 020 R003) was approximately 2.0 mL per dose that contained approximately [redacted] mg of sucrose, approximately [redacted] mg of sodium citrate, approximately [redacted] mg of sodium phosphate, [redacted] mL of tissue culture medium, and no greater than [redacted] mg of polysorbate 80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 in approximately 2.0 mL of buffer/stabilizer with a measured aggregate potency of 8.81 X 10^7 Infectious Units (IU)/dose, 8.01 X 10^7 IU/dose, and 6.91 X 10^7 IU/dose for Lot 1, Lot 2, and Lot 3, respectively.

The placebo (Lot No. PV260 VAO 022 P001) was approximately 2.0 mL per dose that contained approximately [redacted] mg of sucrose, approximately [redacted] mg of sodium citrate, approximately [redacted] mg of sodium phosphate [redacted] mL of tissue culture medium, and no greater than [redacted] mg of polysorbate 80.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA:

Immunogenicity: Antibody responses (SNA Postdose 3 GMTs against rotavirus serotypes G1, G2, G3, G4, and P1 and serum anti-rotavirus IgA) to RotaTeq™/placebo were evaluated in all subjects. These assays were performed on one serum sample collected from each subject approximately 42 days Postdose 3. In addition, Predose 1 serum samples were to be collected in a subset of approximately 140 subjects (approximately 40 subjects per vaccine lot and approximately 20 subjects in the placebo group) at predetermined study sites. Predose 1 serum samples were assayed for SNA against rotavirus serotypes G1, G2, G3, G4, and P1.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and diarrhea.

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5.3.3 Discontinuation of Subjects From Therapy or Study Observation

A subject was considered to have completed the study when he/she had at least: (1) Received all 3 scheduled vaccinations; and (2) Completed at least 42 days of safety follow-up after each vaccination. Reasons for premature withdrawal from the study were recorded on the worksheets [3.5].

5.4 Treatments

5.4.1 Treatments Administered

The protocol designated 4 treatment group assignments, 1 group for each of the 3 lots of RotaTeq™ and 1 group for placebo. Table 5-3 (Section 5.4.2.1) summarizes the dosage and potency administered to subjects enrolled in each treatment group.

The protocol directed that each subject receive 3 oral doses of RotaTeq™ or placebo administered in 3 separate visits scheduled 4 to 10 weeks (28 to 70 days) apart (dose intervals were calculated based on date of dose = Day 1). The first dose was administered between 42 and 84 days of age (age was calculated based upon date of birth = Day 1). The formulation of vaccine used in this study did not require prefeeding the subject prior to administration.

5.4.2 Identity of Clinical Supplies

5.4.2.1 RotaTeq™ and Placebo

Each dose of RotaTeq™ contained human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 and was supplied at a potency within the range of the final release potencies, in the final formulation, and in the final container intended for the licensed product. Placebo was supplied in an identical container. The estimated final volume/dose of RotaTeq™ was approximately 2 mL, and the potency range was (b) (4) infectious units (IU)/reassortant/dose to (b) (4) (b) (4) IU/reassortant/dose, (b) (4) IU/dose. The potency for each of the consistency lots was targeted for the middle of the range; the actual potencies ranged from 6.91 x 10^7 IU/dose to 8.81 x 10^7 IU/dose. The potencies of the 3 lots of RotaTeq™ were measured using a multivalent quantitative polymerase chain reaction assay (M-QPA) which measures the potency of each reassortant serotype. The total potency/dose is calculated as the sum of the potencies of each of the individual reassortants. A description of this assay can be found in Section II.11.4. The vaccine was a buffered, liquid product that was ideally stored at 2 to 8°C. The formulation

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used in this study, when fully characterized, contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate 80. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) µg/dose. Trace components of fetal bovine serum may also have been present.

Each dose of placebo was approximately 2 mL in volume, consisting of approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate 80

RotaTeq™ and placebo were supplied in the final container representative of that intended for the marketed product, which was packaged in a foil pouch. This container consisted of a plastic dosing tube with a twist-off cap, allowing for direct oral administration to the infant. The pouch containing the tube was labeled with double-panel blinded labels and contained information similar to the following: control number (control number pertained to shipments that included both vaccine and placebo), AN, storage conditions, dosage instructions "Administer as per Protocol" and cautionary statements, as applicable.

RotaTeq™ and placebo were provided in kits. Each kit was intended for a single subject and contained 3 doses of RotaTeq™/placebo. The kits were labeled with at least the following information: RotaTeq™ Vaccine/Placebo, 3 tubes each containing ~2 mL dose for oral administration, store at 2 to 8°C, AN, protocol number, packaging control number (WP-XXXX), SPONSOR name and address, and applicable caution statements.

Once labeled, RotaTeq™ was indistinguishable from placebo. Thus, upon arrival at the clinical study site, the treatment contained in each kit was blinded to both the investigator and the subject.

Identity of the clinical materials is given in Table 5-3.

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V260
Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine for Oral Administration

CLINICAL STUDY REPORT
I. SYNOPSIS

Quadrivalent Vaccine Containing Serotypes G1, G2, G3, and P1

PROTOCOL TITLE/NO.: Safety, Tolerability, and Immunogenicity of Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine in Healthy Adults — #001

INVESTIGATOR(S)/STUDY CENTER(S): Paul A. Offit, M.D., Philadelphia, PA, U.S.A.

PRIMARY THERAPY PERIOD: 19-Jun-1993 to 08-Jul-1993; Clinical Data Cutoff Date: 04-Dec-1996; Serology Cutoff Date: 11-Nov-1996; Study Completion Date: 08-Jul-1993.

CLINICAL PHASE: I

DURATION OF TREATMENT: Single dose/14-day follow-up.

OBJECTIVE(S): Primary Objective: To determine if the vaccine is safe in healthy immune adults. Secondary Objective: To investigate immune responses after a single dose of quadrivalent vaccine when administered orally to healthy adults.

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial.

SUBJECT ACCOUNTING:

	Rotavirus Vaccine	Placebo
ENTERED: Total	20	11
Male (age range-years)	10 (22 to 40)	5 (21 to 42)
Female (age range-years)	10 (19 to 47)	6 (22 to 34)
COMPLETED:	19	11
DISCONTINUED: Total	1	0
Clinical adverse experience	0	0
Laboratory adverse experiences	0	0
Refused further participation	1	0

DOSAGE/FORMULATION NOS.: Regimen: A 1.0-mL dose of vaccine/placebo orally administered, following an 8-hour overnight fast. One-half hour before administration, subjects were given 4 teaspoons of MAALOX™ (magnesia alumina oral suspension antacid, Novartis Consumer Health, Inc.) to ensure uniform gastric buffering and were asked to refrain from eating for 1 hour after administration of vaccine/placebo. Clinical Material: Quadrivalent human-bovine rotavirus reassortant vaccine, Lot 1340A/C-Y560A, 1.2-mL vial. This vaccine contained serotypes G1, G2, G3, and P1 each with an estimated final titer of 1 x 10^7 plaque-forming units (PFU)/mL in (b) (4) Medium (b) (4) (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4). Placebo, Lot 1341/C-Y561, 1.2-mL vial. This placebo contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4), and (b) (4) at (b) (4)

DIAGNOSIS/INCLUSION CRITERIA: Healthy adults 18 years of age or older who had no: known hypersensitivity to any component of the rotavirus vaccine, e.g., (b) (4); known or suspected impairment of immunologic function; fever, ≥100°F (oral) at the time of immunization; clinical evidence of chronic or active gastrointestinal illness prior to immunization; other vaccines given within 14 days prior to administration of study vaccine; history of drug or alcohol abuse. Subjects were not pregnant or expecting to conceive during the study period. Subjects must have agreed to use an acceptable method of birth control for 2 weeks after the immunization. Abstinence was considered an acceptable method of birth control. Subjects did not have any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA: Immunogenicity Evaluation: Serum neutralizing antibody levels (for each of G1, G2, G3, P1, bovine WC3 strain, and human W179 strain specificities). Safety Evaluation: Incidence of serious vaccine-related adverse experiences (Days 0 to 14 postvaccination); fecal vaccine virus shedding (Days 2 to 7 postvaccination); temperature elevations (Days 0 to 14 postvaccination); and serum alanine transaminase (ALT) levels (Days 0 and 14 postvaccination).

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CSR SYNOPSIS (CONT.)
Protocol 002

V260
Live Quadrivalent Human-Bovine Rotavirus Reassortant Vaccine.
Oral Rotavirus Gastroenteritis

DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each dose was 1.0 mL of quadrivalent G1, G2, G3, and P1 human-bovine reassortant rotavirus vaccine or placebo. Dose 1 was given on Day 0, Dose 2 was given 6 to 8 weeks after Dose 1, and Dose 3 was given 6 to 8 weeks after Dose 2.

Clinical Trial Material: G1, G2, G3, and P1 serotype of human-bovine rotavirus reassortants, with an estimated final titer of 4 X 10^7 plaque-forming units (PFU), Lot No. 1340A/C-Y560A. Placebo represented buffer alone; i.e., without quadrivalent human-bovine rotavirus reassortants, Lot No. 1341/C-Y561. Vaccine and placebo contained (b) (4) Medium (b) (4) with (b) (4) at (b) (4) at (b) (4) and (b) (4) at (b) (4) Trace components of fetal bovine serum and (b) (4) may have been present in the vaccine and placebo.

CLINICAL MATERIAL:

Vaccine	Lot Number-Fill Number	Dosage	Potency (PFU/dose)	Package
Live rotavirus vaccine	1340A/C-Y560A	1.0 mL	4 x 10^7	Code-labeled vial kept at (b) (4)
Placebo	1341/C-Y561	1.0 mL	0	Code-labeled vial kept at (b) (4)

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 2 to 6 months of age who had no known or suspected impairment of immunologic function; no prior administration of any rotavirus vaccine; no fever (defined as a rectal temperature of ≥100.4°F) at the time of immunization; no history of chronic diarrhea or failure to thrive; no clinical evidence of active gastrointestinal disease; no other vaccines given within (+/-) 14 days of any dose of vaccine; no condition that, in the opinion of the investigator, could have interfered with the evaluation of the study objectives; and no infant who resided in a household with an immunocompromised individual.

EVALUATION CRITERIA: **Efficacy:** The case definition for rotavirus gastroenteritis was that a subject must have met both of the following criteria: (1) ≥3 watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting. (2) Rotavirus must have been identified in a stool specimen taken within 14 days of the onset of symptoms. **Immunogenicity:** Serum samples, taken Predose 1 and Postdose 3, were tested by enzyme immunoassay (EIA) for serum neutralizing antibody (SNA) against G1, G2, G3, P1a, P1G1, G6, and P7. Serum was also tested for anti-rotavirus IgA and IgG. Stool samples, taken Predose 1 and Postdose 3, were tested for fecal anti-rotavirus IgA and total fecal IgA, as well as for fecal neutralizing antibody (FNA) against G1, G6, P1a, and P7. **Safety:** The subjects' parents/guardians were asked to record any adverse experiences that occurred within 14 days after any vaccination. Temperatures were recorded daily for 7 days after each administration of vaccine/placebo. Stool samples for viral shedding were obtained from all participants between Day 3 and Day 5 after Dose 1. In addition, the Philadelphia study site collected stool samples for vaccine viral shedding 1 to 2, 3 to 5, 7 to 9, and ~15 days following each dose.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The primary efficacy hypothesis that the quadrivalent rotavirus vaccine provides efficacy against rotavirus disease throughout one rotavirus season was tested using an exact conditional procedure. The primary hypothesis in the protocol refers to 80% efficacy, which is the expected efficacy that was used for power and sample size calculations; however, the primary hypothesis was tested for vaccine efficacy >0.0% relative to placebo, as noted in the Data Analysis Plan (DAP). A point estimate and exact two-sided 95% confidence interval for vaccine efficacy were also calculated. In order for the quadrivalent rotavirus vaccine to be declared efficacious (i.e., in order to reject the null hypothesis), the lower bound on the confidence interval for vaccine efficacy had to exceed 0%. If there were 160 evaluable infants per group, and assuming that the true incidence of disease in the placebo group would be 10% and that the vaccine would be 80% efficacious in the prevention of rotavirus disease, there would be 80% power to reject the primary null hypothesis. One hundred eighty (180) evaluable infants per group would provide 80% power with an attack rate as low as 9% in the placebo group.

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CSR SYNOPSIS (CONT.)
Protocol 003

V260
G1 G2 Reassortant Rotavirus
Vaccine Live (Human-Bovine)
Oral
Rotavirus Gastroenteritis

SUBJECT ACCOUNTING:

	Rotavirus (G1, G2) Vaccine				Placebo (Groups 2, 4, 6, and 8 Combined)
	1.0 mL – No Buffer (Group 1)	1.0 mL – 1x Buffer (Group 3)	2.5 mL – 1x Buffer (Group 5)	1.0 mL – Conc. Buffer (Group 7)	
ENTERED: Total	142	150	147	142	150
Male (age range—weeks)	64 (8 to 21)	74 (8 to 21)	76 (6 to 21)	77 (8 to 21)	79 (8 to 21)
Female (age range—weeks)	78 (6 to 21)	76 (8 to 21)	71 (7 to 21)	65 (8 to 21)	71 (8 to 21)
COMPLETED:	136	138	137	132	138
DISCONTINUED: Total	6	12	10	10	12
Clinical adverse experience	0	1	0	2	2
Refused further participation	3	6	6	5	6
Lost to follow-up	3	5	4	3	4

DOSAGE/FORMULATION NOS.: Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of administration was either 1.0 mL or 2.5 mL, depending upon the subject's group assignment. Each dose was provided under the following schedule:
Dose 1, given on Day 0.
Dose 2, given between Days 42 and 56.
Dose 3, given between Days 84 and 98.

Group	Prefeeding	Vaccine Vol (mL)	Buffer/Stabilizer	PFU/Dose
1	Yes	1.0	None	1x 10^7 PFU
2†	Yes	1.0	None	0
3	No	1.0	1x	1x 10^7 PFU
4†	No	1.0	1x	0
5	No	2.5	1x	1x 10^7 PFU
6†	No	2.5	1x	0
7	No	1.0	Concentrate	1x 10^7 PFU
8†	No	1.0	Concentrate	0

† Placebo.

CLINICAL MATERIAL: G1 and G2 human-bovine reassortant rotavirus vaccine, a live virus vaccine, Lots No. 1507/W-D152, 1493/W-C971, 1494/W-C972, and 1495/W-C973. The vaccine contained serotypes G1 and G2, each with an estimated final titer of 5 x 10^6 PFU/reassortant or a total of 1x10^7 PFU G1 and G2 human-bovine rotavirus reassortant vaccine per dose, in (b) (4) Medium (b) (4) (b) (4) Placebo represented buffer alone; i.e., without rotavirus vaccine, Lots No. 1506/W-D151, 1489/W-C967, 1490/W-C968, and 1491/W-C969.

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CLINICAL STUDY REPORT
I. SYNOPSIS

V260
G4 Human-Bovine Reassortant
Rotavirus Vaccine, Oral
Rotavirus gastroenteritis

PROTOCOL TITLE/NO.: Safety and Tolerability of Oral, Live G4 Human-Bovine Reassortant Rotavirus Vaccine in Healthy Adults and Healthy Infants #004

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (02) U.S.

PRIMARY THERAPY PERIOD: 19-Mar-1998 to 07-Jul-1998 (last dose of therapy).
Study completed: 18-Aug-1998.
Clinical Case Report Form and Laboratory Data In-House Cut-off Date: 10-Sep-1999.

CLINICAL PHASE: IIb

DURATION OF TREATMENT: Single dose/42-day follow-up.

OBJECTIVE(S): To assess that the G4-reassortant rotavirus vaccine is generally safe and well tolerated, in order to include it in a multivalent oral live rotavirus vaccine.

STUDY DESIGN: Double-blinded, placebo-controlled randomized study organized in 2 stages. Stage 1 was conducted in healthy adults; Stage 2 was conducted in healthy infants, after subjects from Stage 1 had been followed 14 days without any vaccine-related serious adverse experiences. Within each stage, subjects were randomized between vaccine and placebo groups at a ratio of 2:1.

SUBJECT ACCOUNTING:

	Adults (Age Range in Years)			Infants (Age Range in Weeks)		
	Rotavirus (G4 Vaccine)	Placebo	Total	Rotavirus (G4 Vaccine) Vaccine	Placebo	Total
ENTERED: Total	10	5	15	47	23	70
Male (age range)	6 (26 to 53)	3 (23 to 30)	9 (23 to 53)	25 (8 to 21)	13 (9 to 21)	38 (8 to 21)
Female (age range)	4 (27 to 54)	2 (28 to 32)	6 (27 to 54)	22 (9 to 21)	10 (8 to 21)	32 (8 to 21)
COMPLETED:	10	5	15	46	22	68
DISCONTINUED: Total	0	0	0	1	1	2
Clinical adverse experience	0	0	0	0	0	0
Deviation from protocol	0	0	0	0	0	0
Refused further participation	0	0	0	0	0	0
Lost to follow-up	0	0	0	1	1	2

DOSAGE/FORMULATION NOS.:

Regimen: A single, 1-mL dose of clinical material, vaccine or placebo, was administered orally to each subject on Day 0. The vaccine was given approximately one-half hour after the administration of a buffering agent.

Clinical Trial Material: The vaccine contained G4 human-bovine reassortant rotavirus with an estimated final titer of 10^7 plaque-forming units (PFU) in a 1-mL dose. The vaccine composition included (b) (4) Medium (b) (4) at (b) (4) at (b) (4) at (b) (4) and sucrose (b) (4), Lot No. V260-OSO-001-D001. Trace components of fetal bovine serum may also have been present in the vaccine. The placebo was composed of (b) (4) Medium (b) (4) at (b) (4) at (b) (4), and Sucrose (b) (4), Lot No. 1506/W-D151.

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DOSAGE/FORMULATION NOS.:

Regimen: Three (3) doses of the clinical material were administered to each subject orally. The volume of each vaccination was 2.0 mL of vaccine or placebo. Vaccination 1 was to be administered on Day 1, Vaccination 2 was to be administered 28 to 70 days after Vaccination 1, and Vaccination 3 was to be administered 28 to 70 days after Vaccination 2.

Clinical Material: RotaTeq™ at expiry potency (Lot Nos. V260 VAO 019Q001 and V260 VAO 019Q002) contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, (b) (4) mL of tissue culture medium, and no greater than (b) (4) mg of polysorbate-80, and human-bovine rotavirus reassortants G1, G2, G3, G4, and P1 with an estimated final aggregate potency of ~1.1 x10^7 infectious units (IU)/dose in approximately 2.0 mL of buffer/stabilizer. Theoretical calculation of (b) (4) material (b) (4) was (b) (4) µg/dose. Trace components of fetal bovine serum may have also been present.

The placebo (Lot No. PV260 VAO 009A009) was approximately 2.0 mL per dose that contained approximately (b) (4) mg of sucrose, approximately (b) (4) mg of sodium citrate, approximately (b) (4) mg of sodium phosphate, and no greater than (b) (4) mg of polysorbate-80.

DIAGNOSIS/INCLUSION CRITERIA: Healthy infants, 6 through 12 weeks of age, who had no known history of congenital abdominal disorders, intussusception, or abdominal surgery; no known or suspected impairment of immunological function; no known hypersensitivity to any component of the rotavirus vaccine; no prior receipt of any rotavirus vaccine; no fever, with a rectal temperature ≥38.1°C (≥100.5°F) at the time of immunization; no history of known prior rotavirus disease, chronic diarrhea, or failure to thrive; no clinical evidence of active gastrointestinal illness. (Note that infants with gastroesophageal reflux disease [GERD] were permitted to participate in the study as long as the GERD was well controlled with or without medication.); no receipt of intramuscular, oral, or intravenous corticosteroid treatment within the 2 weeks prior to vaccination; did not reside in a household with an immunocompromised person; no prior receipt of a blood transfusion or blood products, including immunoglobulins; no receipt of oral poliovirus vaccine (OPV) during the course of the study or within 42 days prior to the first dose of vaccine/placebo; any infant who could not be adequately followed for safety by telephone or home visit; and no condition, which, in the opinion of the investigator, may have interfered with the evaluation of the study objectives.

EVALUATION CRITERIA:

Efficacy: The case definition for rotavirus gastroenteritis required subjects to meet both of the following criteria: (1) 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting, and (2) Rotavirus detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms. All rotavirus-positive stools were evaluated for serotype identification by polymerase chain reaction (PCR). Only naturally-occurring rotavirus AGEs caused by the human rotavirus G- serotypes in the vaccine were included in the primary analysis.

Immunogenicity: In a subset of approximately 175 subjects, antibody responses to the vaccine were evaluated by several assays. Serum samples were collected before Dose 1 and approximately 42 days after Dose 3. Serum was tested by modified enzyme-linked immunosorbent assay (ELISA) for serum neutralizing antibodies (SNA) against the rotavirus serotypes contained within the vaccine (G1, G2, G3, G4, P1, and WC3 (the WC3 serotype is also characterized as G6 and P7[5] throughout this document)). Serum anti-rotavirus IgA was also evaluated.

Safety: The subjects' parent/legal guardians were asked to record any adverse experiences that occurred within 42 days following any vaccination. The subjects' parent/legal guardians were instructed to record daily for the first 7 days following vaccination the subject's temperature, behavioral changes, and the number of episodes of vomiting and/or diarrhea.

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Product: V260
Protocol/Amendment No.: 009-00 24

E. STUDY DESIGN (CONT.)

(WPS&E) department of Merck Research Laboratories (MRL) will also maintain a copy of the unblinded allocation schedule to assist with emergency unblinding, if needed.

Description of RotaTeq™: RotaTeq™ will be supplied at a potency within the range of the final marketed release potencies, in the final formulation, and in the final container. Placebo will be supplied in an identical container. The estimated final volume/dose of RotaTeq™ will be ~2 mL, with a potency release range between (b) (4) IU/reassortant/dose and (b) (4) (b) (4) IU/reassortant/dose, (b) (4) IU/dose. The formulation in which RotaTeq™ is suspended contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80. (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

Description of the Placebo: Placebo is ~2-mL dose that contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no greater than (b) (4) mg polysorbate 80.

b. Special Handling Requirements

Once labeled, RotaTeq™ will be indistinguishable from placebo. Both the vaccine and placebo used in this study will be provided in 5.5-mL labeled oral dosing tubes containing ~2 mL of product. Each RotaTeq™/placebo shipment will include a temperature monitoring device ((b) (4) or similar device) to record vaccine temperature during shipping. The recorders must be removed and deactivated **immediately** upon arrival of the shipment. The temperature-monitoring device must be returned to the SPONSOR. See Appendix 2 for detailed instructions.

The RotaTeq™/placebo should be placed in the refrigerator at 2 to 8°C immediately after arrival, and should be stored refrigerated until needed for administration. A refrigerator temperature log, recording the daily minimum and maximum temperatures, must be maintained at the site. The log will be reviewed throughout the course of the study by the site field monitors. Refrigerator temperatures should be from 2 to 8°C for RotaTeq™/placebo storage. Should the refrigerator temperature reach above 8°C [46.4°F] or (b) (4) the SPONSOR (MPC) should be notified immediately and the RotaTeq™/placebo should not be used.

RotaTeq™/placebo should be administered within 30 minutes of being removed from refrigeration. Study personnel should contact their MPC if this time limit is exceeded.

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E. STUDY DESIGN (CONT.)

Description of RotaTeq™: RotaTeq™ will be supplied at a potency within the range of the final marketed release potencies, in the final formulation, and in the final container. Placebo will be supplied in an identical container. The estimated final volume/dose of RotaTeq™ will be ~2 mL, with a potency release range between (b) (4) IU/reassortant/dose and (b) (4) (b) (4) IU/reassortant/dose, (b) (4) IU/dose. The formulation in which RotaTeq™ is suspended contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and no > (b) (4) mg polysorbate 80. (b) (4) is present in a vaccine dose. Trace components of fetal bovine serum may also be present.

Description of the Placebo: Placebo is ~2-mL dose that contains (b) (4) g sucrose, (b) (4) citrate, (b) (4) phosphate, (b) (4) mL tissue culture medium, and > (b) (4) mg polysorbate 80.

b. Special Handling Requirements

Once labeled, RotaTeq™ will be indistinguishable from placebo. Both the vaccine and placebo used in this study will be provided in 5.5-mL labeled oral dosing tubes containing ~2 mL of product. Each RotaTeq™/placebo shipment will include a temperature monitoring device (b) (4) or similar device) to record vaccine temperature during shipping. The recorders must be removed and deactivated **immediately** upon arrival of the shipment. The temperature-monitoring device must be returned to the SPONSOR. See Appendix 2 for detailed instructions.

The RotaTeq™/placebo should be placed in the refrigerator at 2 to 8°C immediately after arrival, and should be stored refrigerated until needed for administration. A refrigerator temperature log, recording the daily minimum and maximum temperatures, must be maintained at the site. The log will be reviewed throughout the course of the study by the site field monitors. Refrigerator temperatures should be from 2 to 8°C for RotaTeq™/placebo storage. Should the refrigerator temperature reach above 8°C [46.4°F] or (b) (4) the SPONSOR (MPC) should be notified immediately and the RotaTeq™/placebo should not be used.

RotaTeq™/placebo should be administered within 30 minutes of being removed from refrigeration. Study personnel should contact their MPC if this time limit is exceeded.